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Disease-a-Month

Gastrointestinal Malabsorptive Syndromes

WADE VOLWILER

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Disease-a-Month Series

RECENT AND FORTHCOMING ISSUES

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Wade Volwiler

is Associate Professor of Medicine and Head of the Division of Gastroenterology at the University of Washington School of Medicine. He received his M.D. degree from Harvard University, his house staff training at the Massachusetts General Hospital and his advanced subspecialty and research training at the Massachusetts General Hospital and the Mayo Foundation. Dr. Volwiler's special interests are liver diseases and physiology of the liver, metabolism of plasma proteins, clinical conditions associated with abnormalities of plasma protein metabolism, and malabsorption.

DEFINITION

THE LUMEN of the small intestine is, in reality, a huge mixing pool—exchange of fluids, electrolyte and nutrient compounds going on in both directions across the intestinal epithelial surface. The net balance of movement of materials into the body is termed absorption. *Mal*absorption implies a sufficiently inefficient transfer into the body of nutrient compounds so that fecal losses exceed those of the normal. At times, the rate of transfer into the body may be markedly slowed without excessive fecal loss resulting, the small intestine being able to compensate for this inefficiency by virtue of its great length.

Malabsorption of nutrients may result from (1) inadequate biochemical preparation of materials for absorptive attention, (2) uncontrolled rate of delivery of nutrients to the small intestinal lumen, (3) lack of adequate contact time between nutrients and a normally absorbing intestinal surface or (4) biochemical and structural defects of the intestinal mucosal cells. Occasionally, also, there may be competition for use of ingested nutrients by bacteria under circumstances of unusual intestinal disease which allow intraluminal overgrowth.

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Malabsorptive defects may be either specific as regards a single chemical compound, or broad and diffuse, involving multiple nutrients. A striking example of the former is pernicious anemia, wherein the stomach fails to produce the intrinsic factor, a substance essential for conditioning vitamin B_{12} for intestinal absorption. Selective malabsorption from primary intestinal causes of folic acid, vitamin B_{12} or iron has been identified in rare instances. *Even though a marked impairment of absorption of a specific nutrient may predominate, adequate scrutiny of a patient usually demonstrates that the malabsorptive syndrome affects most of the important nutrient compounds.*

The broad malabsorptive syndromes characteristically exhibit their most striking defects in the malabsorption of fat and fat-soluble materials. It has been somewhat easier to measure excessive losses of fat than losses of other types of compounds, and therefore the term steatorrhea (excessive fecal fat loss) has become synonymous with most states of gastrointestinal malabsorption. Steatorrhea in the human adult is defined as a loss of greater than 5% of ingested fat. Often this balance is referred to in terms of the "coefficient of absorption," calculated as follows:

$$\frac{(\text{Gm. ingested fat} - \text{Gm. excreted fat}) \times 100}{\text{Gm. ingested fat}}$$

In normal adults, the coefficient of absorption is 95% or greater, regardless of the amount of fat ingested.

BIOCHEMISTRY OF FAT DIGESTION AND ABSORPTION

The principal processes involved are, in order: (1) Efficient mechanical mixing of ingested fat with bile and pancreatic juices —fluids containing substances which biochemically condition lipids for absorption by the small bowel. (2) Emulsification of fats into small colloidal droplets, thereby yielding a maximal surface for the action of pancreatic lipase. Bile salts have long been recognized as important emulsifiers. Recently, it has been recognized that monoglycerides produced during lipolysis are also of importance. (3) Lipolytic action of lipase causing degradation of triglycerides to monoglycerides and free fatty acids. The most

plentiful and efficient lipase is that from the pancreas. Relatively little is known about the lipase present in the exocrine secretion of the small intestine; the amount is currently believed to be negligible, and simply extruded from the rapidly desquamating intestinal epithelial cells. (4) Transport of lipids across the surface epithelial cells of the small intestine. (5) Transport of absorbed lipids in collecting lacteals and portal venous capillaries. Fatty acids with chain links in excess of 10 carbon atoms are routed as triglycerides by way of the intestinal lymphatics, whereas fatty acids of shorter length are transported in the portal capillary drainage. (6) Excretion of lipid into the lumen of the gastrointestinal tract. This is considered negligible in amount, and probably comes chiefly from the desquamating epithelial cells.

Recent studies indicate that fatty acids can be absorbed satisfactorily whether introduced into the intestinal lumen as triglycerides or as free fatty acid. Intraluminal lipolysis of triglyceride has been shown to proceed in stepwise fashion successively through diglyceride and monoglyceride to fatty acid. Proceeding in parallel with lipolysis, new ester-glyceride bonds may be formed, reincorporating free fatty acids into glycerides. However, the general direction of triglyceride hydrolysis proceeds toward eventual complete separation of fatty acid constituents. Existing evidence indicates that either monoglycerides or free fatty acids are readily absorbed, but not di- or triglycerides. Though there is experimental demonstration that any lipid which can be made into a sufficiently fine emulsion may at times cross the intestinal mucosal wall without molecular alteration, this mechanism of lipid absorption is generally considered of minor importance.

The chemical nature of the fat ingested influences greatly its efficiency of absorption. Malabsorptive defects are most likely to be observed if the dietary fat contains a high proportion of saturated long chain fatty acids, unsaturated fats being more readily absorbed.

Though the contribution of bile and pancreatic juice greatly improves the efficiency of intestinal absorption of lipids, it has been well proved that the complete absence of either one of these digestive juices may still allow 30–70% absorption of dietary lipid provided the gastrointestinal tract is in its normal continuity.

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Malabsorptive states vary widely in severity from conditions so mild as to require extremely elaborate intake-excretion balance studies for recognition to those so severe as to be obvious and even life-threatening.

Until recently, to detect malabsorption, the practicing physician had accessible chiefly tests for the efficiency of absorption of lipids. These are still the most practical and widely used to identify generalized malabsorptive syndromes.

Tests for steatorrhea may be divided into two groups: (1) screening tests for detecting rather obvious gross steatorrhea, which have about an 80% accuracy, and (2) somewhat cumbersome and elaborate intake-excretion balance studies, which are required for greater reliability. Only the latter can accurately detect the milder degrees of steatorrhea. Screening tests include the following: (1) Odor and gross appearance of stool: an experienced observer generally finds unmistakable the rancid odor of excessive free fatty acids and the silvery gray or creamy color which are characteristic of severe steatorrhea. (2) Microscopic stain for neutral fat and soaps: this is a relatively inaccurate test, valuable only in the hands of experienced personnel. Regardless of the etiology of the steatorrhea, most of the fecal fat is present in the form of soaps. Therefore, preparations made for demonstrating only neutral fat are useless. To the fecal sample to be tested, glacial acetic acid is added, and the mixture heated to induce hydrolysis of soaps to free fatty acids. While still in the melted state, the droplets of liberated free fatty acids will stain readily with the Sudan lipid dyes. The sample must therefore be inspected while warm and before drying has occurred. (3) Serum or plasma carotene concentration: values less than 75 μg. per 100 ml. reflect either malabsorption or prolonged lack of ingestion; if the latter is the explanation, a daily oral dose of 20,000 units of carotene in oil for a week will raise the previously low plasma concentration to normal.

"Tolerance" tests, wherein one attempts to measure a rise in blood concentration following oral ingestion of a nutrient, are grossly inaccurate and should probably be abandoned. Such

"absorption tests" pretend to measure the rate rather than the total amount of an orally administered substance absorbed, and are unpredictably affected by variations in gastric emptying time, distribution among the various body fluid compartments, metabolism and organ storage, release from cellular depots and re-excretion into the intestinal lumen as well as the urine. Flat curves may be observed in 5–10% of normal persons, and there is considerable overlap between the range of normal and that for the mildly to moderately steatorrheic.

Whenever available, the more reliable intake-excretion semi-balance tests are far preferable to the foregoing. For lipid compounds, two types of tests are currently in vogue: (1) chemical measurements of fecal fatty acids in 3- or 4-day stool collections while ingesting a relatively constant dietary intake of fat and (2) analysis of fecal radioiodine in 2- to 3-day stool collections following ingestion of radioiodine-labeled triolein or oleic acid. The first of these is a well-established and reliable procedure. In fact, it is so trusted that the method is used as a standard of reliability when determining the accuracy of all other lipid-absorption tests. For the detection of moderate to severe steatorrhea, it is unnecessary that dietary fat be carefully controlled, a wide fluctuation between 70 and 110 Gm. of daily intake yet allowing rather accurate separation of malabsorptive subjects from normals. The diet is usually administered for a 5-day period, the stools being collected for the last 3 days of this program. Shortcuts in the laboratory analysis of aliquots can safely simplify analysis by the well-known method of van de Kamer and associates. Normal subjects on such a program excrete less than 8 Gm. of fatty acids daily. Rather wide fluctuations on successive days in steatorrheic subjects are commonly observed when conducting the test in this manner, but separation from the normal group is still reliable and clear-cut. The radiotriolein test is a modified intake-excretion balance observation, which does not require any attention to diet, except for the preparation of the liquid, emulsified "test breakfast." Giving of the preparation in test capsules is claimed to

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yield unreliable results in subjects having increased rates of gastrointestinal motility or gastric resection. The correlation with chemically analyzed intake-excretion studies has been found disappointing in about 20% of subjects tested simultaneously with both methods. Until further information accumulates, this test can therefore be accepted only with some reservation. Normal subjects are supposed to excrete in feces less than 5% of the orally taken radioiodine.

Recently developed tests for absorption of nonlipid substances of especial interest include the following: (1) Determination of urinary, fecal or hepatic radiocobalt following an oral tracer dose of radiocobalt-labeled vitamin B_{12} given with and without intrinsic factor. (2) Determination of fecal radioiron following an orally given dose. (3) Determination of fecal folic acid loss after ingestion of a measured quantity. This procedure requires a rather meticulous microbiologic assay for folic acid. (4) Quantitation of d-xylose in a 5-hour urine collection following oral administration of a test dose. Though preliminary reports have claimed a high degree of diagnostic usefulness for the d-xylose test, it is well known that this pentose is partially metabolized by the human body. Probably overlaps between the milder malabsorptive states and the normal ranges will be discovered, so that it seems best to consider this procedure as a screening test with a probable 80% accuracy.

PATHOPHYSIOLOGY OF CLINICAL SIGNS AND SYMPTOMS

Clinical manifestations of the broad malabsorptive syndromes, and the presenting complaints of such patients, are highly variable. The characteristic pathophysiology of the development of the characteristic clinical signs and symptoms is depicted in Figure 1. This diagram shows that at least 12 different problems may present themselves: hemorrhagic phenomena, diarrhea, tetany, osteomalacia and/or osteoporosis, general malnutrition, edema, amenorrhea, megaloblastic or iron-lack anemia, glossitis and cheilosis and peripheral neuritis.
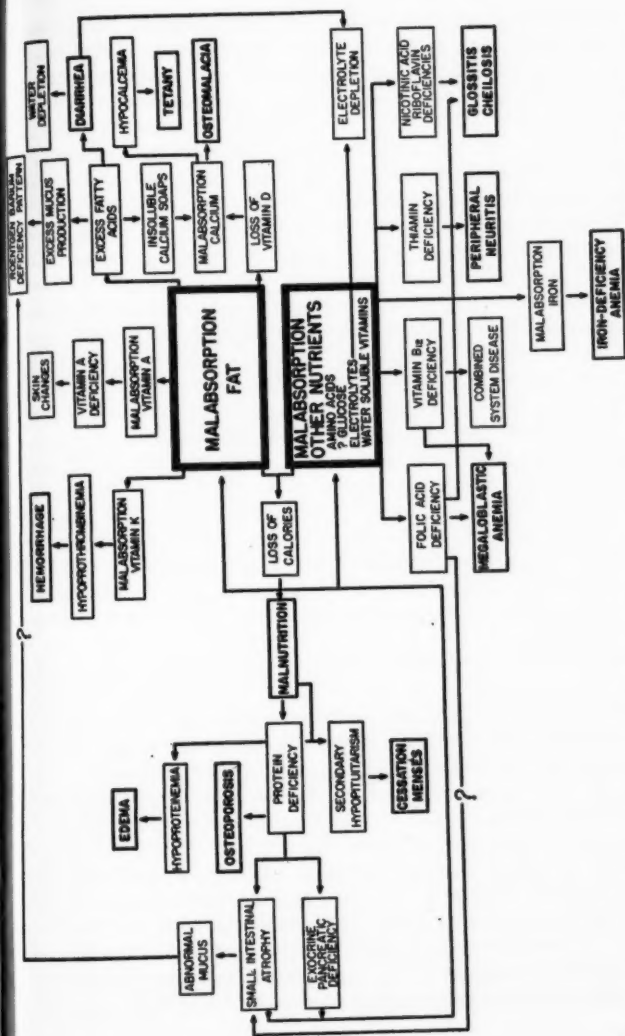
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Fig. 1.—Results of small intestinal malabsorption. (From Volwiler, W.: Gastrointestinal malabsorptive syndromes, Am. J. Med. 23:250, 1957.)

Steatorrhea is always present during exacerbations. As the absorptive defect increases in severity, simple water-soluble compounds may also become poorly absorbed, and manifestations of their lack thus appear. Great variation in the selectivity of such defects has been found. In fulminant sprue, there may appear to be almost no absorption of nutrients ("intestinal shutdown"); even ingested water is retained in the lumen along with unabsorbed osmotically active compounds.

Of special interest are recent investigations concerning the roentgenbarium pattern of the small intestine in steatorrheic states. The classic changes of this "deficiency pattern" include dilatation, segmentation and scattering of barium suspensions, abnormal motility, apparent thickening of folds, "moulage" sign and an increase in intraluminal content of fluid. It has been demonstrated that most of these abnormalities are caused by precipitation of the colloidal barium sulfate by the intraluminal content of fluid and mucus. Chemical abnormalities of gastric and small intestinal mucus have been discovered in sprue, and these may also influence the degree of flocculation of barium sulfate suspensions. In both steatorrheic and normal patients, normal or "deficiency" patterns can be produced at will, depending on the type of barium suspension used. The "deficiency pattern," when observed, does not correlate with the degree of steatorrhea, nor is it diagnostic of any particular variety of such a malabsorptive condition.

Probably the most serious single feature of the broad malabsorption syndromes is the simple loss of calories. Since the adult ordinarily depends primarily on his fat intake for caloric supply, the selectively greater defect in fat absorption will usually manifest itself in progressive weight loss and general malnutrition. As body protein stores are raided for the amino acids then required to provide essential calories through gluconeogenesis, additional malfunction of small intestinal mucosal and pancreatic acinar cells may result. Inadequacy of amino acids for normal synthesis of polypeptide hormones may produce secondary hypopituitarism with resultant cessation of menses in young females.

The metabolic bone disorder resulting from severe, prolonged steatorrhea is usually a mixed bone lesion. Disorders both in (1) formation of bone matrix from protein depletion (osteoporosis)

and (2) demineralization from the long-standing negative calcium balance (osteomalacia) can be expected to be present. At times, the latter may occur without symptomatic hypocalcemia (tetany); presumably a low concentration of ionized serum calcium levels is prevented by compensatory increased parathyroid activity. It has been suggested that such secondary hyperparathyroidism may further increase bone demineralization. Although commonly recognized as a threatening feature of chronic sprue,
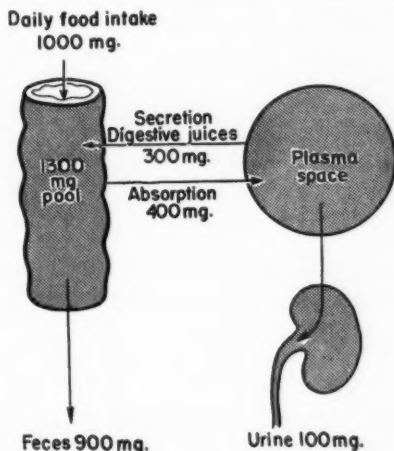
Fig. 2.—Intestine and calcium homeostasis; normal subject.

osteomalacia may result from any variety of severe continuing steatorrhea; for example, it has even followed subtotal gastrectomy for benign ulcer.

Recent studies with radiocalcium by Laszlo and associates have emphasized the critical role of intestinal absorption of calcium in the regulation of the body's total supply of this mineral. Normally, the intestinal epithelium absorbs just that amount required to maintain the body's steady daily requirement, even though the intestinal lumen may contain a large pool of calcium from both diet and secreted digestive juices (Fig. 2). In cases of sprue, negative calcium balance appears to result from a combination of at

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least three factors: (1) an increase in the amount of calcium-containing digestive secretion poured into the small bowel lumen, (2) decreased reabsorption of this endogenous calcium and (3) decreased absorption of dietary (exogenous) calcium (Fig. 3). It has long been known that excessive fatty acids passing down the intestinal lumen "trap" calcium, and that increasing dietary

Daily food intake
1000 mg.

Secretion
Digestive juices
600 mg.

Plasma
space

1600
mg
pool

Absorption
200 mg.

Feces 1400 mg.   Urine 100 mg.
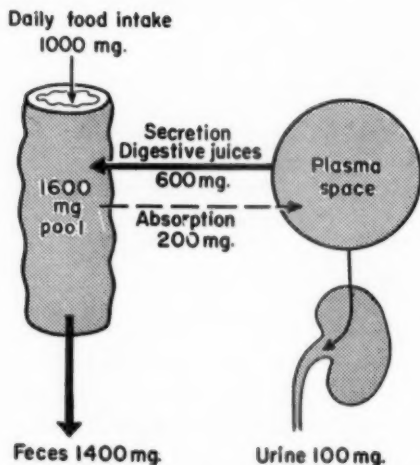
Fig. 3.—Steatorrhea and calcium loss.

fat in states of steatorrhea will thereby increase proportionally the fecal calcium loss.

The hematologic defects of these malabsorptive disorders are protean. In typical sprue or celiac disease, iron-deficiency anemia and megaloblastic anemia may be observed singly or in combination; iron, folic acid and vitamin B_{12} are all poorly absorbed. Megaloblastic anemia due to vitamin B_{12} malabsorption can regularly be expected to develop after total gastrectomy, due to absence of intrinsic factor, but is not thought to result from partial gastrectomy unless gastric mucosal atrophy also occurs. Folic

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acid or vitamin B_{12} deficiency may arise from a variety of other small intestinal disorders (blind loops, diverticula, strictures) in which an abnormal overgrowth of intestinal bacteria appears to compete with the host for these ingested compounds.

Usually, iron-lack anemias following gastrectomy are primarily the result of depletion of iron stores before or in association with the surgery, with inadequate replenishment, and the anemia of most of these patients responds well to orally given medicinal iron supplements. Recent studies with radioiron indicate that absorption of food iron in some cases is often subnormal, and this observation seems to explain some of the prolonged iron-deficiency syndromes in those which have not been vigorously treated with medicinal iron. Usually nonresponse to oral medicinal iron reflects a broad type of malabsorptive syndrome.

GASTRECTOMY

Malabsorptive defects following gastric surgery are complex and not yet thoroughly understood. It appears that the pyloric "gate" is a most important functioning structure in absorption, regulating the rate of loading of the small intestinal lumen with foodstuffs (Fig. 4). Any operative procedure destroying this regulating mechanism places a tremendously increased challenge on small intestinal efficiency. Much of the inefficiency of absorption following gastric surgery appears due to inefficiency of mixing of food with bile and pancreatic juices (Fig. 5). However, despite these suppositions, the administration of supplements of commercial bile salts and/or pancreatic extracts to such patients has been utterly disappointing. Giving maximal size to the remaining gastric reservoir and retaining gastroduodenal continuity are helpful in minimizing malabsorptive losses following gastrectomy. All total gastrectomized patients have gross steatorrhea. From 20 to 50% of humans in published studies of Billroth II subtotal gastrectomy were demonstrated to have steatorrhea; an adequately large series studied with random selection has not yet been published.

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PANCREATIC INSUFFICIENCY

Exocrine insufficiency of the pancreas occurs in all degrees. Since this organ has a large reserve capacity, important nutritional defects do not result until its exocrine activity is almost entirely missing. Thus, even severe, diffuse disease of this organ may be present without absence of duodenal enzymes or presence of absorptive defect. Even after removal of the head of the gland or complete surgical extirpation of it in adult human subjects, a large share of dietary nitrogen and fat can be absorbed, and this is true even if partial gastrectomy also has been performed. Fecal losses of fat and nitrogen in achylia pancreatica have been found to be no greater than in other types of malabsorptive syndromes herein discussed.

The enzyme content of exocrine pancreatic secretion is rather sensitively influenced by dietary protein intake. Normally, the daily quantities of enzyme protein manufacture are large, and the rate of uptake of labeled amino acids by the acinar cells is extremely rapid. It is not surprising, therefore, that protein malnutrition suppresses formation of pancreatic enzymes. Extreme protein lack, as in kwashiorkor, eventually results in necrosis and atrophy of the acinar cells. In addition, a lack of specific acids in the lumen of the upper small intestine may prevent adequate release of pancreozymin, which is necessary to stimulate production of pancreatic enzymes.

HEPATOBILIARY DISEASE

The regular occurrence of steatorrhea during obstructive jaundice has long been recognized. Lack of bile salts in the intestinal lumen results in malabsorption of all lipid compounds, including fat-soluble vitamins such as vitamin K. Thus, for years, surgeons have emphasized the importance of administering vitamin K-active compounds routinely to jaundiced patients being prepared for surgery. In long-standing biliary cirrhosis, steatorrheic losses of vitamin D and calcium may cause osteomalacia. That reduction in such losses of fecal fat may be brought about by returning the patient's own bile to his intestinal tract is accepted. However, little can be accomplished by giving commercial bile salt prepara-
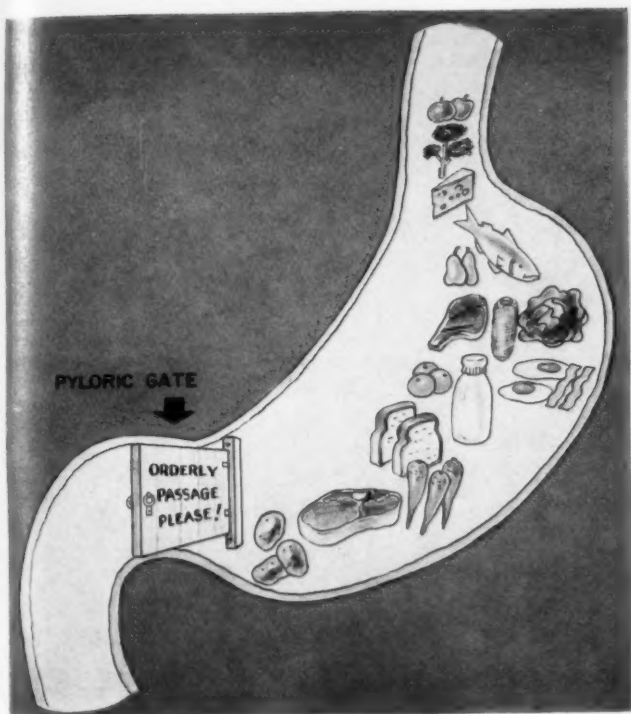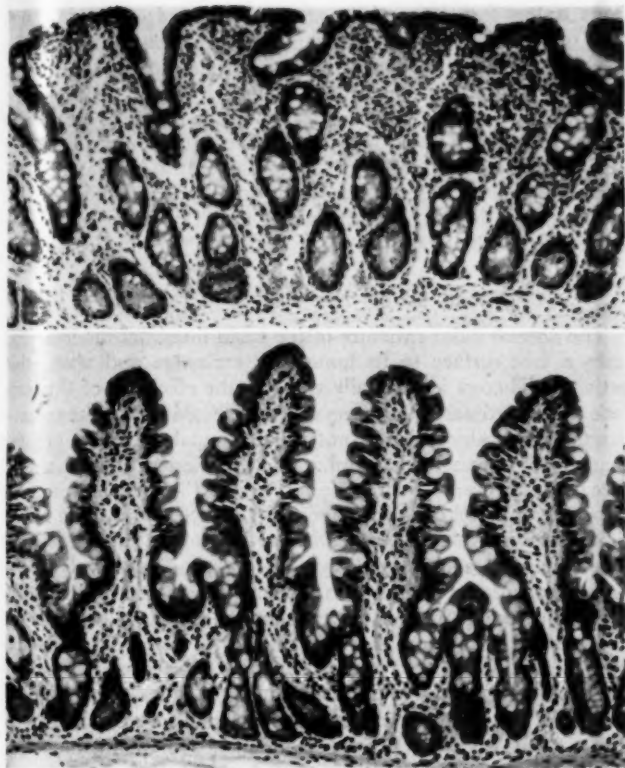
Fig. 4.

Fig. 5.

Fig. 6.—Jejunal biopsy of adult celiac (above) and normal subject (below). Note clubbing, thickening and disappearance of villi in full-blown celiac syndrome, resulting in marked decrease of surface epithelium. (Courtesy of Dr. Cyrus E. Rubin.)

tions unless large quantities are administered; even in huge quantities, some bile salt compounds have been shown to be completely ineffective. Since synthesis of bile salts by the liver is sensitively suppressed by hepatic injury, it would naturally be expected that resultant steatorrhea would be found in most cases of severe primary liver disease, whether acute or chronic. Fat intake-excretion studies have clearly demonstrated that this occurs. However, malabsorption is not usually considered a major problem in primary hepatic diseases unless a strong degree of biliary stasis exists chronically.

DISORDERS OF THE SMALL INTESTINE

The normal villar structure of the small intestinal mucosa presents a vast surface to its lumen for exchange and absorptive activities. Though individually variable, the efficiency of this surface is extraordinary, and normally is protected by a great reserve length. Thus, absorption is not usually impaired unless greater than 50% is resected, assuming the remainder to be normal. Occasionally, even short remaining lengths (3–7 feet) of normal upper small bowel can suffice for maintenance of adequate nutrition. Metabolic rates of biochemical activity of the small intestinal epithelium are surprisingly rapid. The rate of renewal of the surface mucosal epithelial cells is about the most rapid for any body cells, the entire surface undergoing complete turnover in less than 3 days in man. This high rate of cell turnover is reflected in the rapid uptake of radiolabeled amino acids. Tissue and radioautographic studies have indicated this uptake to be faster in rate for the small intestinal epithelium than for any other body tissue. Obviously, the nutrient requirements for maintenance of an efficient small bowel epithelial surface are enormous. Therefore, logically, the small intestinal epithelium should suffer from protein malnutrition, lack of folic acid, vitamin B_{12} or other compounds crucial to the formation of nucleic acids and cell division, or the presence of metabolic antagonists to these groups of compounds.

Until recently, celiac disease and adult sprue were considered to be disorders of biochemical function of the small intestinal epithelium, without accompanying histologic abnormality. Recent

opportunities through newly developed instruments for biopsy of the small intestinal mucosa have completely changed this concept. Full-blown sprue and celiac syndromes are characterized by atrophy of villar structures, with thinning, clubbing and flattening of villar tufts, resulting in a marked decrease in luminal surface available for exchange and absorption (Fig. 6). Presumably, these histologic changes are preceded by nutritional and biochemical defects in the small intestinal epithelial cells, and in the early stages of some syndromes may be somewhat reversible, although this point remains to be conclusively demonstrated. There is great likelihood that not only are adult nontropical sprue and celiac disease identical entities, but also that these are conferred by genetic factors.

CLASSIFICATION OF MALABSORPTIVE CONDITIONS

The following classification of the broad malabsorptive disorders is based on the major defects in digestion and transport of lipids and therefore on the principal points of the normal biochemical processes involved in fat digestion and absorption:

I. Inadequate mixing of food with bile salts, lipase.
   1. Pyloroplasty.
   2. Gastroenterostomy.
   3. Subtotal gastrectomy.
   4. Total gastrectomy.

II. Inadequate lipolysis—lack of lipase.
   1. Exocrine pancreatic insufficiency.
      a. Congenital cystic fibrosis of pancreas.
      b. Chronic pancreatitis.
      c. Cancer of pancreas or ampulla.
      d. Pancreatic fistula.
      e. Severe protein deficiency.

III. Inadequate emulsification of fat—lack of bile salts.
   1. Obstructive jaundice.
   2. Severe liver disease.

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IV. Primary absorptive defect of small intestine.
1. Inadequate length of normal surface.
   a. Surgical resection.
   b. Internal fistula.
2. Inadequate absorbing surface due to extensive mucosal disease.
   a. Inflammatory—tuberculosis, regional enteritis.
   b. Neoplastic.
   c. Amyloid infiltration.
   d. Scleroderma.
   e. Whipple's disease.
3. Primary biochemical dysfunction of epithelial cells.
   a. Celiac disease.
   b. Sprue.
   c. Severe starvation.
   d. Transient dysfunction associated with intestinal infections.
4. Malabsorption associated with blind loops, diverticula, strictures.

V. Obstruction of mesenteric lymphatics.
1. Lymphoma.
2. Carcinoma.

Although this classification has proved useful as a working basis for clinical differentiation of these groups, it is far too simplified from the standpoint of accuracy in biochemical etiology. Many conditions listed participate in more than one of these categories of derangement. An equally useful classification has been one in which the malabsorptive syndromes due to small intestinal dysfunction have been divided into "primary" and "secondary" sprue syndromes; this latter term would include groups 1, 2 and 4 of division IV of the classification. The exact mechanism by which the presence of blind loops, jejunal diverticula, and so forth, causes malabsorption is not fully determined. But improvement in such syndromes as a result of oral antibiotic therapy has led to the concept that the absorptive defects may be due principally to either (a) competition of intraluminal bacteria with the

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host for nutrients or (b) production locally of antimetabolites by high-lying intraluminal bacteria.

DIFFERENTIAL DIAGNOSIS

Ordinarily, there should be no problem in recognizing the presence of surgical reconstruction of the upper gastrointestinal tract, obstructive jaundice or severe primary hepatic disease. The major difficulties, therefore, arise in differentiating exocrine pancreatic insufficiency from other causes of malabsorption, and in distinguishing the many possible varieties of primary small intestinal lesions.

PANCREATIC INSUFFICIENCY

Proof that inadequacy of the external secretion of the pancreas causes a given malabsorption syndrome is frequently difficult to achieve in the present state of knowledge. The best one can do is to (1) rule out all other causes of malabsorption, (2) make certain the clinical data implicate extensive pancreatic disease strongly and (3) conduct the best laboratory tests for assessing pancreatic exocrine function available, the results of which show compatibility with pancreatic exocrine insufficiency. When ruling out other causes of malabsorption, biopsy of the small intestinal mucosa, demonstrating its normalcy, is probably of great importance; this procedure will be discussed later.

In the adult, exocrine pancreatic insufficiency is usually the result of chronic, recurring pancreatitis; cancer is a far less common cause. A diagnosis of carcinoma of the pancreas currently requires surgical biopsy or positive cytologic identification. It has been shown that careful cytologic examination of duodenal content following secretin injection may yield a positive diagnosis in over 50% of cases. At laparotomy, differentiation from chronic pancreatitis may be extremely difficult, surgical biopsy of a firm pancreas may reveal only a pancreatitis surrounding a carcinoma, and a taking of biopsy always presents a considerable risk of pancreatic fistula unless conducted transduodenally. A recent report

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that serum and urine elevations of leucine aminopeptidase favor a diagnosis of carcinoma of the pancreas is of great interest. Further study may well prove that this test will become a valuable screening guide to selecting cases for more definitive cytologic examination. Chronic pancreatitis is suggested by a characteristic long history of recurring attacks of upper abdominal pain, although some cases run their full course of pancreatic destruction painlessly. A screening roentgen film of the abdomen should always be obtained in these patients, looking for characteristic calcification in the area of the pancreas; however, advanced chronic pancreatitis may be present without such calcifications. The presence of mild diabetes mellitus accompanying steatorrhea strongly suggests simultaneous destruction of both pancreatic islets and exocrine tissue. However, it has been recognized that either insulin production or exocrine secretion may separately become insufficient as the result of chronic pancreatitis.

In children, mucoviscidosis is, of course, a major if not the most important cause of exocrine pancreatic insufficiency. Therefore, when exploring the possibility of exocrine pancreatic insufficiency in children, one should routinely carry out accessory tests of electrolyte concentration in sweat or saliva, and perhaps viscosity measurements of duodenal contents.

Firm laboratory support for proof of pancreatic exocrine insufficiency is as yet somewhat elusive. It is our current belief that the most reliable test for demonstrating *lack* of extensive functional pancreatic destruction is the secretin test; nonresponse strongly suggests exocrine insufficiency. The secretin test is cumbersome and requires experience for reliability; therefore, it is reserved for the select group in which clinical suspicion strongly indicates the possibility of pancreatic insufficiency. One is here testing specifically the ability of the ductular cells of the pancreas to produce a gush of sodium bicarbonate solution in response to the intravenous secretin load. The duodenal collecting tube must be positioned with fluoroscopic check, and the continuous collection of specimens monitored frequently with pH test paper. Periodic emptying of the stomach producing bursts of acid material may occur, and these portions should be discarded. The crucial normal response to be watched for is a marked rise in bicarbonate

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concentration with reciprocal fall of chloride (table); maximal response usually occurs in the first 20 minutes following IV secretin. If the rise in bicarbonate concentration of duodenal fluid

SECRETIN TEST, NORMAL SUBJECT

PERIOD (20 MIN.)	VOL. (ml.)	pH	HCO₃ (mEq./L.)	CL (mEq./L.)
Basal	22	7.8	27	118
Post-Secretin (IV injection 1 unit per kg. body weight)				
(1)	50	8.5	100	48
(2)	45	8.6	83	61
(3)	23	8.1	30	106

reaches 85 mEq./L., one is usually safe in assuming that exocrine pancreatic function is adequate for digestive purposes. So many errors crop up in conducting this test that a positive response of this degree is more reliable than negative or partial responses. The specimens collected from the secretin test may be used simultaneously for cytologic examination for carcinoma cells.

Two additional types of laboratory determinations, less reliable than the foregoing, are: (1) Tests of fasting duodenal juice for proteolytic and lipolytic enzyme content. Usually, concentrations of these enzymes are reduced in states of marked pancreatic exocrine insufficiency, but it is rare to find absence. It is probably simplest to conduct the laboratory screening for presence of proteolytic enzymes with the well-known Andersen gelatin-digestion method. (2) Response to administered pancreatin in large dosage as demonstrated by prolonged and cumbersome quantitative intake-excretion metabolic studies. It has been our experience that in the adult a decrease in the number of daily bowel movements and cessation of diarrhea cannot at all be relied on as proof that oral pancreatin has affected fecal fat and nitrogen losses. In fact, we have commonly noted extremely poor correlation of the number and volume of daily stools with results of quantitative chemical analysis for stool nitrogen and fat. We are

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likewise impressed with relative unresponsiveness to generously given quantities of oral pancreatin even in patients who seem certain by all other extensive criteria to most certainly have severe pancreatic exocrine insufficiency.

Clinical medicine is currently encumbered with a number of traditional tests for pancreatic insufficiency which are not reliable and should be discarded. These include (1) a gelatin film digestion test for proteolytic activity in stools, (2) microscopic examination of feces for muscle fibers, (3) the Schmidt test to identify excessive fecal nitrogen loss and (4) attempts to determine the ratio of neutral fat to soaps in feces. Nitrogen losses are no greater in pancreatic insufficiency than from many other causes of malabsorption. It is now clearly recognized that determination of the ratio of split to unsplit fat in feces is of no value in differentiating pancreatic insufficiency from other types of steatorrhea. Lipolytic enzymes from colon bacteria generally split neutral fat delivered from the upper gastrointestinal tract.

Recently, with the use of radioiodine-labeled triolein and oleic acid, somewhat successful attempts have been made to demonstrate that in pancreatic exocrine insufficiency orally taken oleic acid may be far more efficiently absorbed than a triglyceride (triolein). It should be emphasized again that counting of fecal losses in such tests is far more reliable than measuring blood concentrations of absorbed materials. Extensive further data is required for an adequate appraisal of this new test.

Small Intestinal Diseases

Differentiation among the major groups of small intestinal disorders is often accomplished adequately by roentgen examination of the small intestine with barium sulfate; usually, barium enema is needed for adequate inspection of the terminal ileum. However, extensive involvement of the small intestine with lymphoma, Whipple's disease, scleroderma, sarcoid and amyloid may occur without roentgenographic evidence. Furthermore, all these disorders may smolder for months or even years in a state masquerading as primary sprue. Therefore, ideally, histologic identification is needed, as accomplished either by small intestinal biopsy

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through intubation or by means of surgical laparotomy. Several devices have recently been made for obtaining mucosal biopsy from the small intestine through intubation. Those most flexible and which bite cleanly no deeper than muscularis mucosa appear most satisfactory (Crosby capsule, Rubin tube). Extreme care must be used for properly orienting specimens obtained before sectioning; otherwise, great confusion in interpretation is likely. Jejunal samples are less misleading than duodenal specimens. This opportunity to obtain multiple biopsies of the small intestine in various disorders of man has come so recently that it is not yet possible to appraise adequately the full scope of usefulness and limitations of this valuable method. However, it is already clear that characteristic gross and microscopic appearance of villar atrophy is observed in full-blown celiac and adult sprue (Fig. 6), which easily separates most of these disorders from other causes of malabsorption. The sampling of the small intestine by these methods is so spotty that a positive diagnosis of one of the regional small intestinal disorders having localized or "skip" involvement can be obtained only through extreme luck, and surgical laparotomy is still often necessary for identification.

The findings of peripheral or mediastinal lymphadenopathy and sacro-iliac arthritis have been helpful in identifying Whipple's disease, and the diagnosis has been made by peripheral lymph node biopsy. The development of chylous ascites in association with steatorrhea indicates inflammatory or, more usually, neoplastic obstruction of the cisterna chyli or of the major collecting lacteals in the mesentery. Although cytologic examination of such peritoneal fluid can occasionally identify carcinoma, surgical exploration with direct biopsy is generally required for certain diagnosis.

ROUTINE LABORATORY INVESTIGATIONS

All patients with recognized gross malabsorption syndromes should have certain routine laboratory and roentgen examinations, and many of these should be repeated regularly during therapy.

All new cases should have a roentgen survey film of the abdomen for detecting calcification in the region of the pancreas.

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Likewise, all patients should have adequate roentgen studies of the small intestine with barium sulfate suspensions. If it is deemed important to outline the terminal ileum, barium enema is usually required. All patients should have a routine small intestinal mucosal biopsy by intubation, if available. Currently, it is believed that, when properly conducted, this procedure clearly separates full-blown sprue and celiac disorders from other causes of gross malabsorption.

If a gross steatorrhea has been present for longer than 1 year, a base-line roentgen survey of spine, pelvis and chest for bony rarefaction should be made. In obtaining these films, accessory diagnostic features relating to some specific causes of malabsorption syndromes may be discovered, such as mediastinal lymphadenopathy in lymphoma, and mediastinal lymphadenopathy and sacroiliac arthritis in Whipple's disease.

If hematocrit and appraisal by blood smear of the erythrocytes indicate anemia, bone marrow examination for determining the state of iron stores and megaloblastic activity is warranted. Low plasma prothrombin concentration even in the absence of ecchymosis may suggest inadequacy of absorption of vitamin K; prompt response from low to normal values after injection of menadione is confirmatory. Serum total protein and albumin concentrations are important in appraising the degree of protein malnutrition and the capacity of the body to maintain the homeostatic mechanisms supporting the plasma protein levels. A selective fall in serum albumin is characteristic of starvation syndromes. Determination of serum calcium, phosphorus and alkaline phosphatase is indicated in steatorrheic syndromes of prolonged duration to discover if hypocalcemia or osteomalacia is present. The adequacy of the ionized serum calcium concentration must be determined by a comparison of the total serum calcium with the serum total protein and albumin concentrations. Osteomalacia, as evidenced by an increased serum alkaline phosphatase activity, may develop despite a normal serum calcium concentration. This situation has been attributed to response of the parathyroids to a previously decreased serum calcium. A low-serum phosphorus concentration, which is often present, may reflect decreased renal tubular reabsorption of phosphate attributable to parathyroid overactivity. Impaired absorption of phosphorus from the intestine may also

contribute. A urine Sulkowitch test, or 24-hour urine calcium excretion, provides a crude reflection of the serum ionized calcium concentration, and is therefore somewhat useful as a measure of hypocalcemic tendency or an indication of overdosage with vitamin D. Occasionally, a striking exception to this generalization may occur in patients rapidly repairing a severe osteomalacia, wherein urine Sulkowitch tests can remain persistently negative for long periods following the return to normal of the low-serum calcium. Presumably, this reflects a strongly positive calcium balance occurring during bone remineralization. If available, determination of per cent absorption of radiocobalt-labeled vitamin B_{12}, radioiron and folic acid may be helpful in understanding the scope of the absorptive defect and providing more specific therapeutic implications.

THERAPY

GENERAL CONSIDERATIONS

Certain general therapeutic principles apply to all gross steatorrheas, regardless of etiology. General support and rehabilitation of body nutrition is the cornerstone to treatment. In severe cachexia, prolonged parenteral supplementation may be required to supply both calories and amino acids. The oral dietary recommendations allow considerable variation in daily fat intake. Since it has been demonstrated that loss of fecal fat from mixed dietary fats is usually proportionate to total oral intake, a larger amount of dietary fat yields greater net absorption of fat than would a low-fat intake. The added calories may be of advantage despite increased steatorrhea. The level of dietary fat must, however, be tailored to the individual patient, for most steatorrheic subjects experience increasing diarrhea as their fat intake is raised; a daily intake of approximately 70 Gm. is generally chosen. If annoying diarrhea is present, fat restriction to 40 Gm. or less daily is advisable.

To protect the patient with chronic steatorrhea from hypoprothrombinemia, daily oral water-soluble vitamin K derivatives are required (menadione, 5–10 mg.) ; rarely, this compound must be injected to guarantee absorption. Patients with continuing gross

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steatorrhea require protection also against osteomalacia; calcium balances are usually negative. To correct this situation, extremely large intakes of *both* calcium and vitamin D are generally required to achieve a positive calcium balance. One is then constantly fraught with the potential of inducing vitamin D poisoning on the one hand, or prolonging the negative calcium balance and drain on bone minerals on the other. Calcium supplements can be provided satisfactorily in almost any available form of calcium, including large amounts of skimmed milk. In ordering supplements of calcium lactate and gluconate, it is important to recognize that these compounds contain a small proportion of calcium, and therefore supplements of 5–10 Gm. daily of these whole compounds are generally needed. Patients with gross steatorrhea tolerate vitamin D orally quite well, and an oral dosage of 25,000–600,000 units daily of the oily form over prolonged periods is commonly required. The administration of water-miscible vitamin D emulsions, injectable vitamin D preparations or ultraviolet radiation of the skin may be useful, although these approaches are usually unnecessary. The amount of vitamin D given must be adapted to the severity of the tetany, osteomalacia or steatorrhea, and the patient must be constantly examined to avoid over- or underdosage. Frequent repetition of the urine Sulkowitch test and determinations of serum calcium, phosphorus and alkaline phosphatase levels are indicated.

Anticholinergic drugs, such as Pamine®, Banthine® or Pro-Banthine®, tend to reduce abnormal gastrointestinal motility in some steatorrheic patients and therefore are somewhat useful to decrease painful peristaltic spasm; oral calcium carbonate may do likewise. Opiates, because of the potential problems of addiction in chronic disease, should be used with great caution.

The evidence that fat absorption can be improved by the addition of oral emulsifying agents, such as Tween® 80, as extensive data has now accumulated, is quite disappointing, and such supplements are no longer considered worthwhile.

Since folic acid and vitamin B_{12} are such essential materials for the normal rapid cell division of the small intestinal epithelium, it seems wise to provide regular supplements of these compounds to any patient with gross malabsorption. A daily oral ration of 5–10

mg. of folic acid and monthly injections of 20–50 μg. of vitamin B₁₂ are suggested.

Iron-lack anemias generally necessitate replenishment of iron stores by injectable iron preparations; oral iron may be non-absorbed. If the malabsorptive defect is diffuse and severe, and involves simple water-soluble compounds, supplementation with oral or parental vitamin B complex and vitamin C may be needed. Extreme states of sodium and potassium losses are commonly observed in sprue syndromes with marked watery diarrhea; in such patients water deficits may also result.

SPECIFIC DISEASE GROUPS

POSTGASTRECTOMY SYNDROMES.—Malnutrition in most of these conditions is not due primarily to true malabsorptive defects. It is the result of inability to eat normal quantities of food because of (a) feelings of early fullness in the small gastric reservoir or (b) the "dumping" syndrome. Therapeutic strategy is therefore directed toward increasing total caloric intake with limited bulk, but its success is unfortunately limited. Relatively small-sized meals should be provided 5–7 times daily, and the amount of readily soluble, osmotically active nutrients, such as sugars, icings and syrups should be limited. For those patients having, in addition, true malabsorptive defects (all total gastrectomies, 10–50% of partial gastrectomies, some simple pyloroplasties), no specific drugs have been found regularly helpful. Even supplements of large quantities of pancreatic extracts and commercial bile salt preparations have been regularly disappointing. Adrenal steroids and ACTH have not been helpful.

It must be emphasized that all patients who have had a near-total gastrectomy should receive regular parenteral supplements of vitamin B₁₂, since absence of intrinsic factor from the stomach prevents normal absorption of this compound, leading eventually to a pernicious anemia syndrome.

EXOCRINE PANCREATIC INSUFFICIENCY.—Only in this condition has pancreatin been consistently demonstrated to be of value. Commercial preparations are frequently impotent in enzyme activity. Probably dosage should vary somewhat with the severity

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of the exocrine deficiency; a range of 5–15 Gm. daily is thought needed in adults. At best, provision of this amount will approximately halve the fecal fat and nitrogen losses. A variable response to these agents has previously been mentioned and in our experience is frequently disappointing. Recently, it has been reported that these supplements are far more effective if divided into hourly amounts starting at breakfast and ending at bedtime. The logic for this approach is that active pancreatic enzymes have a short duration of viability in the small intestinal lumen, and that the supply therefore needs constant renewal during the digestive process. In the human subject, supplements of choline or other lipotropic agents for preventing fatty liver, such as needed in dogs following pancreatectomy, are thought unnecessary.

HEPATOBILIARY DISORDERS.—Supplements of commercial bile salt preparations have not been shown to reduce steatorrhea occurring in these syndromes. Patients with prolonged obstructive jaundice, as in primary biliary cirrhosis, require constant protection against fat-soluble vitamin deficiencies and osteomalacia.

PRIMARY INTESTINAL DISORDERS.—(a) *Massive intestinal resection:* No specific measures combat the malabsorptive defects of this condition. A strenuous effort to increase total caloric intake appears to be the best general approach. Restriction of fat may be unnecessary, and more than moderate restriction is likely to be unwise, since all calories which can be absorbed are badly needed.

(b) *Regional enteritis:* In some instances, adrenal steroids may greatly improve the malabsorptive phenomena. Antibiotics and low-gluten diet have not been found helpful.

(c) *Whipple's disease:* In a number of patients, adrenal steroids have been highly effective, but disappointments are also reported.

(d) *Blind loops and diverticula:* Suppression of bacterial flora through oral chemotherapeutic or antibiotic agents has frequently resulted in improvement of the malabsorptive condition. If the area of involvement is relatively localized, surgical resection should be considered.

(e) *Nontropical sprue and celiac syndromes:* The two most helpful therapeutic agents for these conditions are (1) "gluten-free" diet and (2) adrenal steroids (or ACTH). Most of these

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conditions respond to either. Since the maintenance of these patients for long periods on steroid compounds may have undesirable sequalæ, an effort should be made to induce and maintain remission with a "gluten-free" regimen.

Of the many varieties of cereal glutens, the gliadin fractions of the glutens from wheat and rye seem the principal offenders. The mechanism of their ill-effect in susceptible subjects is unknown. Since small amounts of these polypeptides can induce an exacerbation of malabsorption in celiacs, a "gluten-free" diet program must be meticulously, rigidly and continuously maintained for benefit. Small amounts of wheat or rye flour lurk as additives in many canned or prepared foods. A remission induced by institution of a "gluten-free" program of an acute sprue or celiac syndrome may occur rapidly (1–7 days). In more chronic situations, it is claimed that taking a low-gluten diet continually for 6 or more months may be necessary to induce an improvement. However, *spontaneous* remissions of these disorders may be this frequent.

In acute or resistant chronic sprue or celiac conditions, the administration of steroid drugs (ACTH, cortisone acetate, hydrocortisone, prednisolone) may yield excellent improvement. A sudden and dramatic increase in absorption may occur within 24 hours of initiating such therapy, so as to be considered "life-saving." The presence of nutritional edema is not a contraindication to such use of steroids. The mechanism of improvement by steroids is unknown, but virtually all materials traversing the small mucosal surface may become better absorbed. In comparison with other diseased conditions wherein the nonspecific, anti-inflammatory effects of steroid agents are sought, the primary sprue syndromes are usually excellently regulated by relatively small doses of these drugs; a daily oral maintenance dosage of 25–30 mg. cortisone acetate or 5–10 mg. prednisolone frequently suffices. Relapse commonly occurs 2–3 weeks after omitting steroid therapy.
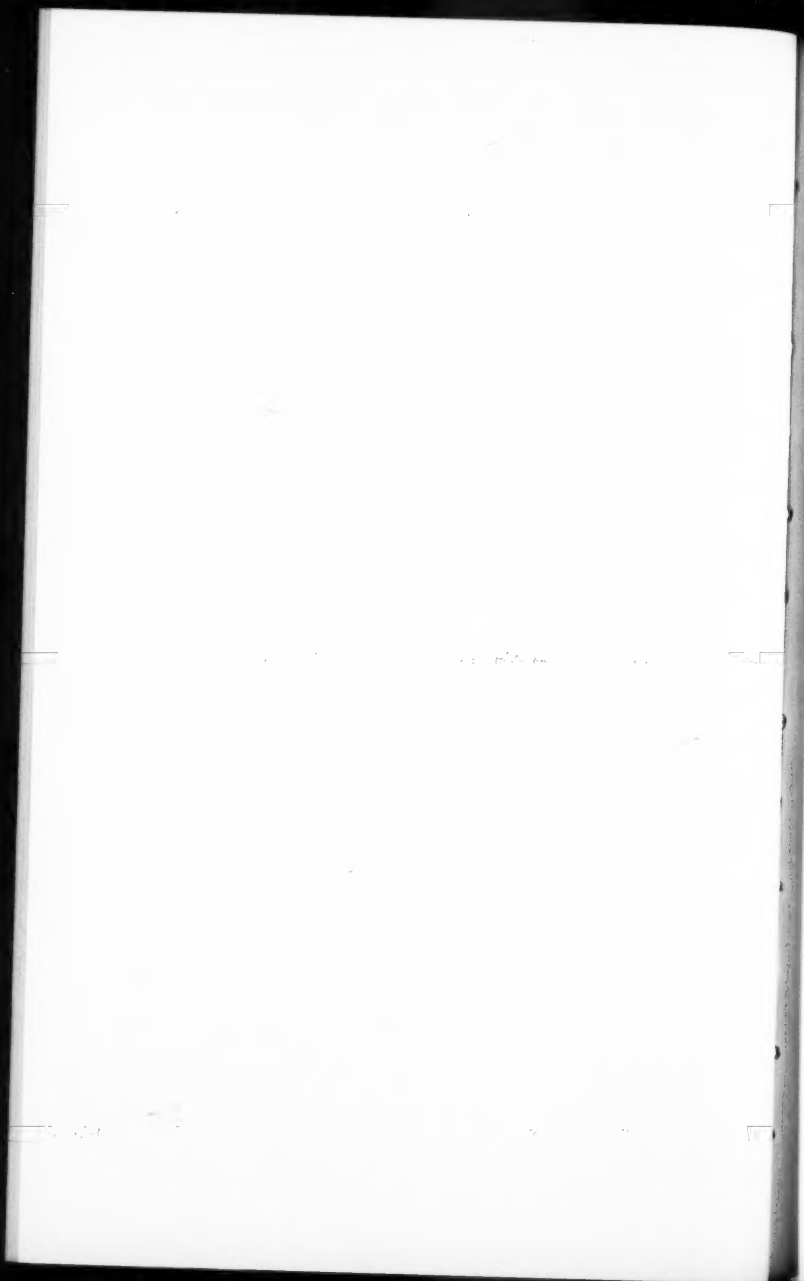
(f) *Tropical sprue:* This is probably a heterogeneous group of disorders, many of them related to variable types of nutritional deficiencies. Folic acid or folinic acid seem almost specifically helpful in many of these disorders, and vitamin B_{12} has sometimes also been useful, but less reliably so. The old, traditional liver

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extracts presumably contained folic acid, folinic acid or vitamin B_{12} as diluted active ingredients. Carefully studied patients have responded dramatically for short periods to orally given chemotherapeutic and antibiotic substances. Low-gluten diets have not yet been demonstrated to provide benefit.

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